In claim 19, line 1, change "18," to --16,--.

In claim 20, lines 1-2, change "second moiety" to --protein--.

REMARKS

Reconsideration of the Official Action mailed June 21, 1996 is respectfully requested.

Upon entry of this Amendment, claims 1, 3-8 and 10-21 will remain pending in this application. Claims 2 and 9 are canceled without prejudice or disclaimer, and these claims support the changes to claims 1 and 15. Additionally, support for the addition of fungal polysaccharides to claims 1 and 15 can be found, for example, at page 16, line 12 of the original specification. No new matter is believed to be included in this Amendment.

I. Objections to the Specification

As suggested by the Examiner in the Official Action, Applicant has updated the status of the applications cited at pages 11, 12 and 20 of the application text. Withdrawal of this objection is respectfully requested.

To more completely advise the Examiner of the status of these applications, Applicant advises that U.S. Patent Application No. 07/834,067, filed February 11, 1992 was abandoned in favor of U.S. Patent Appl. No. 08/126,017, filed September 24, 1993, which was abandoned in favor of U.S. Patent Appl. No. 08/402,565, filed March 13, 1995, which application has been

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allowed. U.S. Patent Appl. No. 08/055,163, filed February 10, 1993 was abandoned in favor of U.S. Patent Appl. No. 08/444,727, filed May 19, 1995, which currently is under final rejection.

With respect to the sequence listing on page 43 of the application, as requested by the Examiner, Applicant submits herewith the sequence listing in compliance with 37 C.F.R. §§ 1.821-1.825. Withdrawal of this objection is respectfully requested.

The content of the Sequence Listing paper attached hereto is the same as the computer readable copies submitted herewith. Furthermore, this Sequence Listing submission contains no new matter.

II. Response to Non-Statutory Double Patenting Rejection

Claims 1-21 are provisionally rejected under the doctrine of obviousness-type double patenting based on claims 22-34 in U.S. Patent Application No. 08/408,717. Because this is a provisional rejection, it is respectfully requested that the requirement for a Terminal Disclaimer be held in abeyance until such time that at least one of the applications is allowed.

III. Response to Rejections Based on 35 U.S.C. §§ 102 and 103

A. Rejections based on Andersson or Rehner

Claims 1-6, 9, 10 and 12 are rejected under 35 U.S.C. § 102(b) as being anticipated by the Andersson et al. article (hereinafter "Andersson"), or Rehner et al., U.S. Patent No. 4,931,392 (hereinafter "Rehner"). These rejections are respectfully traversed and reconsideration is requested.

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Applicant's claim 1 recites an improvement in a method for preparing a vaccine having an immunogenic construct and a pharmaceutically acceptable carrier. In the claimed improvement, the immunogenic construct is produced by (a) activating a viral, fungal or bacterial polysaccharide with an organic cyanylating reagent to form an activated carbohydrate, and (b) coupling the activated carbohydrate directly or indirectly to a protein to form the immunogenic construct that is capable of stimulating an immune response. The organic cyanylating reagent, as recited in claim 1, is selected from the group of 1-cyano-4-(dimethylamino)-pyridinium tetrafluoroborate, N-cyanotriethyl-ammonium tetrafluoroborate, and p-nitrophenylcyanate. Nothing in either Andersson or Rehner teaches or suggests this claimed improvement in a method for preparing a vaccine, because neither Andersson nor Rehner relates to a process for producing a vaccine.

Andersson relates to epidermal growth factor ("EGF") - dextran conjugates that purportedly can be used to deliver toxic radioactive nuclides to EGF receptors of cancer cells. In this manner, cytotoxic agents for treating cancer and the like can be delivered directly to the cancer cells while minimizing adverse effects on normal, non-cancerous tissue in the patient.

Nothing in Andersson teaches or suggests the recited improvement in a method for preparing a vaccine that includes an immunogenic construct and a pharmaceutically acceptable carrier. More specifically, nothing in Andersson teaches or suggests a process for preparing an immunogenic construct that includes activating a polysaccharide with a selected organic cyanylating reagent and thereafter coupling the activated polysaccharide to a protein to form an

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immunogenic construct capable of stimulating an immune response. While Andersson does disclose that dextran can be activated with CDAP and coupled to EGF, nothing in Andersson teaches or suggests that the resultant product is an immunogenic construct capable of stimulating an immune response. Additionally, nothing in Andersson teaches or suggests that the resultant EGF-dextran conjugate may be used with a pharmaceutically acceptable carrier to produce a vaccine. Andersson, quite simply, does not relate to vaccines or immunogenic constructs that are capable of stimulating an immune response.

Accordingly, it is respectfully submitted that Andersson does not anticipate the claimed invention or render the claimed invention *prima facie* obvious. Withdrawal of this rejection is respectfully requested.

Like Andersson, Rehner has nothing to do with processes for preparing a vaccine or an immunogenic construct that is capable of stimulating an immune response. Rehner relates to a process for stabilizing creatine kinase so that the material will maintain a stable, known creatine kinase content and activity over an extended period of time. In this manner, the creatine kinase can be used as a control or calibration solution for chemical analyzers. See, for example, column 1 in Rehner. There is no motivation, teaching or suggestion that the material or process described in Rehner may be used in a process for producing a vaccine. Additionally, there is no motivation, teaching or suggestion in Rehner that the material or process described therein may be used to make an immunogenic construct that is capable of stimulating an immune response.

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Accordingly, Applicant respectfully submits that Rehner does not render the claimed invention unpatentable under either 35 U.S.C. § 102 or § 103. Withdrawal of this rejection is respectfully requested.

B. Rejection based on Handley

Claims 1-6, 9, 10 and 12 are rejected under 35 U.S.C. § 102(e) based on Handley et al., U.S. Patent No. 5,177,059 (hereinafter "Handley"). This rejection is respectfully traversed and reconsideration is requested.

Handley relates to water-soluble polymyxin B-carrier conjugates that are used as antibiotics to neutralize endotoxins. Administration of the conjugates is said to be an improvement over administration of native polymyxin B ("PMB") because the conjugates are less toxic than PMB, but they retain PMB-activity. See, for example, column 2, lines 5-9 and column 4, lines 30-34 in Handley. Nothing in Handley teaches or suggests a process for producing a vaccine including an immunogenic construct and a pharmaceutically acceptable carrier. Furthermore, nothing in Handley teaches or suggests the recited process of producing an immunogenic construct that is capable of stimulating an immune response.

In view of the foregoing, it is respectfully submitted that Handley fails to anticipate the claimed invention or render the claimed invention *prima facie* obvious. Withdrawal of this rejection is respectfully requested.

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C. Rejection based on Dick or Chu in view of Kohn

Claims 1-21 are rejected under 35 U.S.C. § 103 as being unpatentable over the Dick, Jr., et al. article (hereinafter "Dick") or the Chu et al. article (hereinafter "Chu"), in view of the Kohn et al. article (hereinafter "Kohn"). This rejection is respectfully traversed and reconsideration is requested.

Dick relates to glycoconjugates of bacterial carbohydrate antigens. Chu relates to a study of specific protein/polysaccharide conjugates. In the Official Action, the Examiner acknowledges that neither Dick nor Chu teaches the use of organic cyanylating reagents, such as CDAP, CTEA or pNPC, as recited in Applicant's independent claims 1 and 15. Note pages 4-5 of the Official Action.

In an effort to overcome the deficiencies of these primary references, the Examiner relies on the Kohn article. Kohn discloses the use of various cyanylating agents, such as CDAP or CTEA, for activating polysaccharides. Nothing in Kohn, however, teaches or suggests the use of organic cyanylating agents, such as CDAP, CTEA or pNPC, in a process for producing a vaccine, as recited in Applicant's claims. Furthermore, nothing in Kohn teaches or suggests a process for activating a polysaccharide with an organic cyanylating reagent to form an activated carbohydrate and thereafter coupling the activated carbohydrate to a protein to form an immunogenic construct capable of stimulating an immune response, as recited in Applicant's claims 1 and 15.

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The documents relied on by the Examiner fall into two distinct categories. The first category, including the Dick and Chu articles, describe conjugate vaccines. Nothing in these articles teaches or suggests the use of an organic cyanylating reagent to activate a polysaccharide in a process for producing an immunogenic construct, as recited in Applicant's claims 1 and 15. The second category includes the Kohn article. While this article describes the use of organic cyanylating reagents, nothing in this article teaches or suggests the use of such reagents in a process for producing a vaccine or an immunogenic construct that is capable of stimulating an immune response. Nothing bridges the gap between the teachings of Dick or Chu and the teachings of Kohn, i.e., there is no motivation to combine the teachings of Kohn with those of Dick or Chu. Only Applicant's specification provides this motivation and teaching.

Because of the distinct gap in the teachings of these two categories of documents, at best, the Examiner may have established that it would be obvious to try to use organic cyanylating reagents in the production of immunogenic constructs for vaccines. This "obvious to try" basis for a rejection under 35 U.S.C. § 103 has long been held to be insufficient to establish *prima facie* obviousness. See, for example, *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987) and *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Accordingly, it is respectfully submitted that these combinations fail to render the claimed invention *prima facie* obvious. Withdrawal of this rejection is respectfully requested.

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D. Rejection based on Dick or Chu in view of any one of Andersson, Rehner or Handley

Claims 1-21 are rejected under 35 U.S.C. § 103 based on Dick or Chu in view of any one of Andersson, Rehner or Handley. This rejection is respectfully traversed and reconsideration is requested.

All of these documents are described above, and the above comments are incorporated herein by reference. Again, these documents fall into two separate and distinct categories, but nothing bridges the gap between the teachings of these two categories. Dick and Chu, as noted above, describe conjugate vaccines. Nothing in these articles teaches or suggests the use of an organic cyanylating reagent to activate a polysaccharide in a process for producing an immunogenic construct, as recited in Applicant's claims 1 and 15. The second category includes Andersson, Rehner and Handley. While these articles describe the use of organic cyanylating reagents, nothing in these articles teaches or suggests the use of such reagents in a process for producing a vaccine or an immunogenic construct that is capable of stimulating an immune response. Nothing bridges the gap between the teachings of Dick or Chu and the teachings of Andersson, Rehner or Handley, i.e., there is no motivation to combine the teachings of these documents. Only Applicant's specification provides this motivation and teaching.

Because of the distinct gap in the teachings of these two categories of documents, at best, the Examiner may have established that it would be obvious to try to use organic cyanylating reagents in the production of immunogenic constructs for vaccines. As noted above, this

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"obvious to try" basis for a rejection has long been held to be insufficient to establish *prima facie* obviousness. See *Geiger*, *supra.* and *Fine*, *supra.*

Furthermore, it is respectfully submitted that Andersson, Rehner and Handley are not analogous to the art of vaccines and immunogenic constructs. Andersson, as noted above, relates to epidermal growth factor-dextran conjugates that are used as targeted carriers to deliver toxins to cancer cells. Rehner relates to stabilized creatine kinase used as control or calibration sera for chemical analyzers. Handley relates to antibiotics for combating infection. It is respectfully submitted that the person of ordinary skill in the vaccine art would not look to these diverse technologies to find a suitable process for producing an immunogenic construct that is capable of stimulating an immune response for use in a vaccine. *In re Wood*, 599 F.2d 1032, 202 USPQ 171 (C.C.P.A. 1979).

For the foregoing reasons, it is respectfully submitted that this rejection fails to establish that the claimed invention is *prima facie* obvious. Withdrawal of this rejection is respectfully requested.

E. Objective Evidence of Non-obviousness

Assuming *arguendo* that one would believe that the Examiner has established *prima facie* obviousness based on the combinations described above (although Applicant does not concede that *prima facie* obviousness has been established), it is respectfully submitted that the objective evidence of non-obviousness in this case rebuts any presumed *prima facie* showing. In

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accordance with the Supreme Court's holding in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), objective evidence of non-obviousness also must be considered in a patentability analysis under 35 U.S.C. § 103. Evidence of a long felt but unsatisfied need for the invention is one indicia of non-obviousness. A second indicia of non-obviousness relates to evidence of copying of the invention by others, as distinguished from their independent development of the invention. When these factors are considered in view of the evidence of record and attached to this Amendment, any presumed *prima facie* showing of obviousness dissolves.

In this case, the prior art of record relating to conjugate vaccines (namely, the Dick and Chu articles) describe the use of CNBr as an activating reagent. The Examiner contends in the Official Action that Dick recognized the disadvantages of using CNBr (e.g., extreme pH) since at least 1989 (the date of the Dick article). Yet, the Examiner recognizes that Dick did not disclose the use of the recited organic cyanylating reagents, despite the disclosure of such reagents by Kohn in 1984. See page 4 of the Official Action. Furthermore, as recognized by the Examiner on page 5 of the Official Action, Chu, dated 1983, does not disclose the use of organic cyanylating reagents in producing conjugate vaccines. Thus, consistent with the Examiner's analysis of the Dick and Chu references, the vaccine art recognized certain disadvantages to CNBr activation, but prior to Applicant's invention, no one disclosed the use of the recited organic cyanylating reagents in a process for producing an immunogenic construct or in a process for producing a vaccine. It is respectfully submitted that the Examiner's analysis of the documents of record demonstrates a long felt but unresolved need in the vaccine art for

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Applicant's invention. Applicant's satisfaction of this long felt need provides secondary evidence of non-obviousness.

As additional objective evidence of non-obviousness, Applicant submits herewith a copy of E. Konadu, et al., "Synthesis, Characterization, and Immunological Properties in Mice of Conjugates Composed of Detoxified Lipopolysaccharide of *Salmonella paratyphi* A Bound to Tetanus Toxoid, with Emphasis on the Role of *O* Acetyls," *Infection and Immunity*, Vol. 64, No. 7, July, 1996, pp. 2709-2715 (Exhibit 1). This article describes protein/polysaccharide conjugates that are produced using both CNBr and CDAP. On pages 2713-2714 of the article, the authors recognize various advantages of using CDAP over CNBr for producing the conjugate vaccines, e.g., lower pH, no requirement for a spacer, and satisfactory yields. Most notably, however, the authors of this article credit the inventor of this patent application, Dr. Andrew Lees, for providing helpful advice relating to his experience with CDAP. See the Acknowledgments on page 2714 of this article. Dr. Mond, also recognized by the authors in this Acknowledgment, has worked with Dr. Lees on CDAP activation in producing immunogenic constructs.

Thus, the authors of the 1996 article in *Infection and Immunity* (Konadu, Shiloach, Bryla, Robbins and Szu), acknowledge certain advantageous aspects of this invention, as well as the helpful advice of the inventor in using the invention. These authors have extensive experience in the vaccine art, yet they relied on the inventor's advice and used his invention in making their vaccine conjugates. To establish the extensive experience of each of these authors, Applicant

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conducted a DIALOG® on-line search to obtain a listing of articles and conference papers in the vaccine field written by these authors. See the Declaration of Christina Kelley (Exhibit 2), which describes this on-line search. A copy of the search results are attached to the Declaration of Christina Kelley as Exhibits 2D to 2H, and the search results are summarized in the following Table:

TABLE

Author's Name	Number of Articles Located
E. Konadu	5
J. Shiloach	24
D. Bryla	24
J.B. Robbins	151
S. Szu	45

These search results demonstrate that each author, and particularly Drs. Shiloach, Bryla, Robbins and Szu, have multiple articles and conference papers relating to conjugate vaccines. Yet, despite their extensive experience and background in the vaccine art, these authors relied on the teachings of the inventor with regard to using an organic cyanylating reagent to produce an immunogenic construct for a conjugate vaccine. This objective evidence is strong evidence of non-obviousness.

Accordingly, it is respectfully submitted that the objective evidence of non-obviousness rebuts any presumed *prima facie* showing under 35 U.S.C. § 103. For these additional reasons, withdrawal of the rejections based on 35 U.S.C. § 103 is respectfully requested.

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IV. Conclusion

Applicant respectfully submits that this Amendment and the attached evidence obviates all of the outstanding objections and rejections in this case and places the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

If any additional fees are due in connection with the filing of this Amendment, such as additional fees under 37 C.F.R. §§ 1.16 or 1.17, please charge the fees to our Deposit Account No. 06-0916. If an extension of time under 37 C.F.R. § 1.136 is necessary, such an extension is requested. The additional extension fee should be charged to Deposit Account No. 06-0916.

Respectfully submitted,

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By: _____
William F. Rauchholz
PTO Registration No. 34,701

Date: September 23, 1996

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